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TITLE

A 'biology first' approach in perinatal pharmacoepidemiology of autism – potential and pitfalls

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In this issue, Janecka and colleagues¹ conclude that maternal prenatal use of most medications that target specific neurotransmitter systems is not associated with offspring autism. This is a new perspective to consider in view of the hypothesis that there could be adverse neurodevelopmental effects of prenatal medications affecting serotonergic, GABAergic and glutaminergic neurotransmitters. Although results vary,^{2,3} previous studies have warned of potential bias arising from confounding by maternal indications for prenatal drug treatments which is ‘stubbornly’ difficult to resolve.⁴ Janecka and colleagues grouped medications into classes on the basis of each drug’s target neurotransmitter, regardless of the drug’s medical indication, and then estimated autism risk associated with maternal use of a drug in a class targeting a common neurotransmitter. They called this a ‘biology first’ approach to highlight that their autism risk assessment was linked to the drugs’ shared pharmacological effect and functional similarities while disassociated from the underlying indication.

The strategy implemented by Janecka and colleagues is intriguing and warrants careful consideration. For perspective, we illustrate two approaches to tease out associations among medical indications for treatment, drug treatments and outcome. In Figure 1 I., the associations with an outcome are compared across different drugs, with potentially different pharmacological mechanisms but prescribed for the same medical indication. In this scenario, if the associations with the outcome are similar across different drugs (and drug mechanisms) then it suggests possible confounding by the underlying medical indication. In contrast, in Figure 1 II.a., the associations of drug treatments, prescribed for different medical indications but sharing a common pharmacological mechanism, are measured for the same outcome. If associations are similar across the treatments, this suggests that the shared pharmacological mechanism,

regardless of the indication, is the basis for the association between the drugs and the outcome. This strategy is consistent with the concept of 'analogy' described as the 9th Bradford Hill criterion for causal inference with observational data. For example, one could propose to test a mechanism underlying an association between a risk factor and outcome on the basis of its analogy to the same mechanism for which there is strong causal evidence.⁵

For the current study, the primary hypothesis that autism may be associated with a perturbed neurotransmitter system mechanism during fetal development is based on considerable scientific support,⁶⁻⁸ but which has not achieved the level of 'strong causal evidence'. In fact, this study's largely negative findings could be viewed as evidence against the neurotransmitter mechanism hypothesis. One should consider, however, what was tested in the current study. For this study (Figure 1 II.b.), all drugs were collapsed into one or more classes, each class sharing a neurotransmitter target (labeled as Mechanism₁ in Figure 1) and the analysis measured the association between each mechanism (drug class) and outcome (autism). Thus, all medical indications and all prescribed treatments for the indications were collapsed into a single mechanism category, making it problematic to tease out the role of confounding by indication, particularly where one particular type of drug dominated a category. Furthermore, there is potential heterogeneity WITHIN each mechanism category in terms of treatment (e.g., drug dose, bioavailability, timing of administration, adverse effects, etc.). For example, some medications, although acting on the same neurotransmitter target may be used in very different dosages depending on the indication. Some antidepressants are prescribed for neuropathic pain conditions and some antipsychotics for hyperemesis gravidarum, but typically at lower dosage for these indications than those for their psychiatric indications. It is not possible to gauge how the

associations estimated in this study may have been impacted by heterogeneity in the actual 'exposure' to drugs in a single class. Ideally, a strategy closer to that illustrated in Figure 1 II.a. could tease out the effects of variation in these pharmacological properties and treatments on the outcome risk but it is unlikely that the present study had sufficient statistical power to carry out such an analysis.

It would be hasty to conclude also, based on this study's negative findings for specific drug classes, that drugs in the class have no associations with autism because there may be other mechanisms at play, e.g. valproate may impair fetal neurodevelopment via inhibition of histone deacetylases leading to increases in gene expression. Further, it is important to recognize that a full profile of the pharmacological properties of many of the drugs examined in this study is still unknown.

An unexpected finding was the importance of the number of maternal illnesses as a confounder. The authors' acknowledged that the 'active ingredient' which explains the confounding mechanism of this measure remains unknown. The well recognized high psychiatric and somatic comorbidity in persons with autism and risk for autism from high maternal comorbidity as seen in this study may actually reflect a common underlying pathogenesis. Thus, it is plausible that the importance of the maternal illness variable is an indication that the study strategy did not fully account for the complex pathways linking maternal medical indications with autism risk and therefore leading to residual confounding in the study results.

Janecka and colleagues acknowledged that their study was exploratory and we agree their results should be viewed as such. Future work could follow their example in suitably powered studies and

with refinements, as exemplified in Figure 1 to strengthen causal inference. In view of heterogeneous results by cognitive ability in autism, this could be best done by examining autism subgroups which may differ in their susceptibility to a drug exposure.⁹ However, no single strategy may be enough to account for confounding by indication and, in the absence of randomised controlled trials, the above approach may be one of several tools in the epidemiologist's toolbox to seek consistency or 'triangulation' of findings across various methods with different strengths and limitations.¹⁰

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FIGURE TITLE: Strategies to examine associations among medical indications for treatment, treatment and outcome